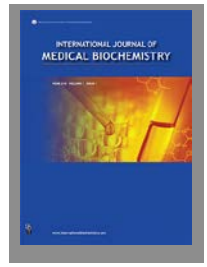
INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2025.59002
Int J Med Biochem 2025;8(2):116–124



Research Article

Association of serum Maresin-1 levels with insulin-resistance indices in obese individuals

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Abstract

Objectives: This study aimed to investigate serum Maresin-1 (MaR1) levels among obese, overweight, and normal-weight groups, as well as to evaluate their association with various metabolic parameters, including insulin resistance-related indices and lipid profiles.

Methods: Ninety subjects were classified into three distinct groups in terms of body mass index (BMI). Using a median MaR1 value of 608 pg/mL as the threshold, the participants were also categorized into two distinct groups. Serum MaR1 levels were quantified via an ELISA. The study also evaluated several other indicators: metabolic score for insulin resistance (METS-IR), triglyceride glucose-body mass index (TyG-BMI), HbA1c, and various components of the lipid profile.

Results: MaR1 levels were significantly lower in the obese and overweight categories compared to the normal-weight categories. Nevertheless, no statistically significant difference was observed in the MaR1 levels between the obese and overweight groups. MaR1 levels were negatively linked to METS-IR ($r=-0.444$, $p<0.001$) and TyG-BMI ($r=-0.427$, $p<0.001$), whereas quantitative insulin sensitivity check index ($r=0.318$, $p=0.002$) levels were positively correlated. METS-IR had the highest AUC value (0.706), with 73.3% sensitivity and 57.8% specificity to identify high levels of MaR1 ($p<0.001$).

Conclusion: Ordinal logistic regression revealed a significant independent relationship between MaR1 levels and BMI categories. The close association between MaR1 and metabolic indices such as METS-IR and TyG-BMI suggests its role in insulin sensitivity and obesity-associated metabolic disorders.

Keywords: Insulin resistance, Maresin-1, METS-IR, obesity, specialized pro-resolving mediators, TyG-BMI

How to cite this article: Deniz L, Yardim M, Saltabas MA, Akkoc RF. Association of serum Maresin-1 levels with insulin-resistance indices in obese individuals. Int J Med Biochem 2025;8(2):116–124.

Obesity is a global medical concern closely linked to chronic inflammation and dysfunctions of carbohydrate metabolism. In obesity, triglyceride accumulation occurs in the adipose tissue, as increased inflammation and insulin resistance promote fatty acid production in the liver. An increase in adiposity in adipose tissue reduces the responsiveness of insulin-sensitive cells to the physiological effects of insulin [1, 2]. In obese patients, adiposity allows the fat tissue to function as an endocrine organ. Adipokines secreted by adipocytes regulate metabolic pathway defects that arise from inflammation and insulin resistance. While numerous molecules have been recognized in this context, research has increasingly concentrated on the impact of new regulatory molecules, including specialized pro-resolving mediators (SPMs), on the obesity-induced metabolic dysfunction [3]. SPMs are bioactive compounds categorized into four primary categories: lipoxins, maresins, protectins, and resolvins [4]. Maresin 1 (MaR1), derived from docosahexaenoic acid (DHA), demonstrates anti-inflammatory in different tissue types, particularly in white adipose tissue. It is synthesized by macrophages through

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Submitted: January 03, 2025 **Revised:** February 05, 2025 **Accepted:** February 07, 2025 **Available Online:** March 06, 2025

enzymatic conversion of DHA via the 14S-hydroxy-DHA and 12-lipoxygenase (12-LOX) pathways [5]. In obesity, elevated free fatty acids activate proinflammatory pathways by upregulating cyclooxygenase (COX) and LOX enzymes, resulting in increased production of mediators such as leukotriene B4 (LTB_4), which recruit neutrophils and exacerbate insulin resistance. This chronic inflammation is further amplified by neutrophil-released cytokines, which disrupt insulin signaling and sustain a proinflammatory state. The resolution of a self-limited acute inflammatory response involves a transition away from generating pro-inflammatory substances, like LTB_4, to the synthesis of counterregulatory substances known as SPMs. To counteract this, MaR1 is synthesized during the resolution phase of inflammation to stop further neutrophil recruitment and promote the clearance of apoptotic neutrophils and debris, thereby preventing chronic inflammation [6, 7].

Although numerous animal studies have explored the relationship between MaR1 and lipid and glucose metabolism, research in humans remains limited. Understanding the role of MaR1 in metabolic regulation is essential for developing effective therapeutic strategies to prevent and manage obesity-related metabolic disorders. This study purposed analyze serum MaR1 levels in patient cohorts stratified into three groups depending on body weight (normal weight, overweight, and obese), and to assess the correlation between MaR1 levels and metabolic indicators.

Materials and Methods

This study was conducted with authorization the Firat University Ethics Committee for Non-interventional Research (Number: 2023/10-23, Date: 27/07/2023). Ninety individuals who attended the Internal Medicine outpatient department at Yerkoy State Hospital between August 2023 and November 2023 were included after obtaining informed consent forms. All stages of the study were carried out conformity the Helsinki Declaration.

This study excluded participants based on the following criteria: age under 18 years, type 2 diabetes mellitus (T2DM), liver diseases, chronic kidney disease, history of bariatric or metabolic surgery, hematological disorders or malignancies, systemic inflammatory or infectious diseases, and use of anti-inflammatory or steroid therapy. Physical examinations were conducted during outpatient assessment, and height and weight measurements were recorded. The participants were grouped into three categories according to their body mass index (BMI): normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) [8]. Additionally, based on the median MaR1 level (608 pg/mL), the study participants were divided into two categories.

Following an 8-hour fasting period, blood specimens have been collected from the participants using serum separator tubes. The samples were allowed to clot for at least 30 minutes before being centrifuged at 2000×g for 10 minutes. The resulting sera were separated, transferred to Eppendorf tubes, and stored at −20°C until analysis. Glucose, alanine aminotransferase (ALT), hemoglobin A1c (HbA1c), aspartate aminotransferase (AST), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels were measured via a Beckman Coulter DxC 700 AU (Beckman Coulter Inc., Brea, CA, USA) clinical chemistry analyzer. Insulin levels were analyzed using a chemiluminescent immunoassay method on a Snibe Maglumi X3 analyzer (Snibe Diagnostics, Shenzhen, China). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was computed via the equation: [glucose (mg/dL) × insulin (mU/L)] / 405 [9]. Metabolic Score for Insulin Resistance (METS-IR) was computed via the equation: Ln [(2 × glucose) + TG] × BMI / Ln [HDL-C] [10]. Body fat percentage (BF%) was estimated using the Deurenberg equation: BF%= 1.2 × BMI (kg/m^2) + 0.23 × age (years) – 10.8 × gender (female= 0, male= 1) – 5.4 [11]. The triglyceride glucose index (TyG), which is considered an effective surrogate marker for insulin resistance, was calculated using the formula: ln [(fasting glucose × TG) / 2]. TyG-BMI was determined by multiplying TyG index by BMI [12]. Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated as follows: 1/(log insulin + log glucose) [13]. The McAuley index was calculated as follows: $=e^{[2.63-0.28\times \ln\ (\text{Insulin})-0.31\times \ln(\text{TG})]}$ [14]. The Castelli risk index (CRI-I) was determined by dividing TC by HDL-C, whereas the CRI-II was derived by dividing LDL-C by HDL-C [15]. The atherosclerotic index (AI) was determined analytically using the formula (TC−HDL-C) / HDL-C [16].

A Human MaR1 enzyme-linked immunosorbent assay (ELISA) (Catalog No: 201–12–7339; Sunred Biotechnology Company, Shanghai, CHINA) was carried out adherence the procedures described in the procedures specified by the manufacturer. The optical density at 450 nm was quantified spectrophotometrically with a CLARIOstar PLUS device (BMG Labtech, Germany). Test results are reported in pg/mL. The measurement range of the MaR1 kit was 7.5 pg/mL to 2000 pg/mL, with a sensitivity of 7.247 pg/mL. The MaR1 kit has an intra-assay coefficient of variation (CV) of less than 10% and an inter-assay CV of less than 12%.

Statistical evaluation

To determine whether the dataset conformed to a normality, Shapiro–Wilk was applied for statistical evaluation. Categorical variables were examined using Pearson's Chi-square test, Continuity Correction, or Fisher's Exact test, depending on the minimum expected count value. When the data did not follow a normal distribution, the Mann-Whitney U was utilized, whereas the Student's t was conducted for data exhibiting normal distribution. To compare three independent groups, ANOVA was performed for normality assumptions, and the Kruskal–Wallis was performed for non-normality assumptions. Post-hoc Tukey or Tamhane's T2 tests were employed for pairwise comparisons among groups following the one-way ANOVA. The correlations between the parameters were assessed using Spearman correlation analysis. ROC analysis was employed to distinguish individuals with high Maresin 1

Table 1. Comparison of demographic and laboratory parameters across the three groups

Parameter	Normal weight (n= 30)	Overweight (n= 30)	Obese (n=30)	p*
Age (years)	39 (31–46)	39 (34–43)	34 (27–43)	0.570
Gender (n, %)				
Male	8 (26.7)	6 (20.0)	7 (23.3)	0.830
Female	22 (73.3)	24 (80.0)	23 (76.7)	
Body mass index (kg/m^2)	23.3 (21.1–24.3)	27.7 (26.4–28.6)^{a1}	31.3 (30.6–34.0)$^{a1, b1}$	**<0.001**
Body fat (%)	29.1 (24.4–31.9)	35.4 (32.3–38.1)^{a2}	39.3 (37.2–43.5)$^{a1, b2}$	**<0.001**
Maresin 1 (pg/mL)	987 (550–2204)	462 (290–1177)^{a2}	480 (380–990)^{a2}	**0.003**
Glucose (mg/dL)	83.2±8.01	88.1±6.88	94.3±8.87$^{a1, b2}$	**<0.001**
Insulin (mIU/L)	8.65 (5.70–11.7)	12.9 (10.3–17.4)^{a2}	19.8 (13.5–32.0)$^{a1, b2}$	**<0.001**
HOMA-IR	1.70 (1.23–2.24)	2.80 (2.40–3.82)^{a1}	4.58 (3.06–7.74)$^{a1, b2}$	**<0.001**
METS-IR	32.4 (29.9–34.2)	41.3 (37.7–44.5)^{a1}	49.4 (45.9–52.9)$^{a1, b1}$	**<0.001**
Triglyceride-glucose index	8.35±0.47	8.57±0.52	8.96±0.51$^{a1, b2}$	**<0.001**
TyG-BMI	192 (176–208)	237 (223–248)^{a1}	284 (275–306)$^{a1, b1}$	**<0.001**
QUICKI	0.36±0.02	0.33 ±0.02^{a1}	0.31±0.02$^{a1, b1}$	**<0.001**
Mcauley index	7.46 ±1.12	6.29±1.23^{a2}	5.02±1.16$^{a1, b1}$	**<0.001**
Hemoglobin A1c (%)	5.23 (5.14–5.50)	5.71 (5.40–5.90)^{a2}	5.90 (5.60–6.20)^{a1}	**<0.001**
Alanine transaminase (U/L)	19.2±6.45	19.5±7.59	18.9±7.33	0.953
Aspartate transaminase (U/L)	20.0 (17.0–23.0)	19.0 (17.2–25.0)	20.5 (17.2–24.0)	0.875
Cholesterol (mg/dL)	187±30.1	179±41.5	203±48.6	0.070
Triglyceride (mg/dL)	101 (79–141)	111 (89–189)	179 (126–224)$^{a1, b2}$	**0.001**
LDL-C (mg/dL)	112 (89–132)	102 (88–127)	132 (98–156)	0.083
HDL-C (mg/dL)	53.0 (47.0–61.0)	45.0 (40.0–60.0)	46.0 (39.0–54.0)^{a2}	**0.031**
TG/HDL-C	2.13 (1.41–2.57)	2.43 (1.53–4.30)	3.51 (2.39–5.39)^{a1}	**<0.001**
Castelli risk index I	3.55±0.77	3.83±1.14	4.56±1.40^{a2}	**0.003**
Castelli risk index II	2.18 (1.55–2.69)	2.16 (1.76–2.76)	2.82 (2.07–3.64)$^{a2, b2}$	**0.006**
Atherosclerotic index	2.55±0.77	2.83±1.14	3.56±1.40$^{a2, b2}$	**0.004**

*: p<0.05: Statistically significant. For pairwise comparisons between the three groups, Bonferroni correction was applied, setting the statistical significance threshold at p<0.017. ^{a}: Comparison with normal weight group; ^{a1}: <0.001; ^{a2}: <0.017; ^{b}: Comparison with overweight group. ^{b1}: <0.001; ^{b2}: <0.017. HOMA-IR: Homeostatic model assessment of insulin resistance; METS-IR: Metabolic score for insulin resistance; TyG-BMI: Triglyceride-glucose index and body mass index; QUICKI: Quantitative insulin sensitivity check index; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG/HDL-C: Triglycerides to high-density lipoprotein cholesterol ratio.

levels. P-value below 0.05 was regarded as statistically significant. However, for pairwise comparisons between the three groups, Bonferroni correction was applied, setting the statistical significance threshold at p<0.017. Statistical analyses were performed and graphs were generated using SPSS v. 26 (IBM Corp., Armonk, NY, US) and GraphPad Prism v. 8.3.0 (GraphPad Software, San Diego, California, US). Post-hoc power analyses were performed using G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

Results

Glucose, insulin, HOMA-IR, METS-IR, TyG, TyG-BMI, HbA1c, TG, TG/HDL-C, CRI-I, CRI-II, and AI were higher in obese individuals than in normal-weight individuals; QUICKI, Mcauley index, and HDL-C were lower in obese individuals than in normal-weights. Insulin, HOMA-IR, METS-IR, TyG-BMI, and HbA1c levels were higher in overweight patients than in normal-weight patients. QUICKI, and McAuley index levels were lower in overweights than in normal-weights. Glucose, insulin, HOMA-IR, METS-IR, TyG, TyG-BMI, TG, CR-II, and AI were higher in obese individuals than in overweight individuals. QUICKI and Mcauley indices were lower in obese subjects than in overweight subjects. MaR1 levels were lower in both the obese [480 (380–990)] and overweight [462 (290–1177)] groups than in the normal-weight group [987 (550–2204)]. The analysis revealed that MaR1 levels did not differ between individuals classified as obese and those classified as overweight (Table 1 and Fig. 1a). A post-hoc power analysis was conducted for Maresin 1 among the BMI groups. The mean and standard deviation values were used to determine the effect size, which was determined to be Cohen's f=0.34, with an alpha of 0.05, a total sample size of 90, and three groups, yielding a power of 0.82. Given that the power exceeded the ideal value of 0.80, it could be concluded that the power was sufficient.

There were no differences in age, sex, glucose, TyG, Mcauley index, ALT, AST, cholesterol, TG, LDL-C, HDL-C, TG/HDL-C, CRI-I, CR-II, and AI parameters between the groups with MaR1≥608 levels and MaR1<608 levels. BMI, BF%, insulin,

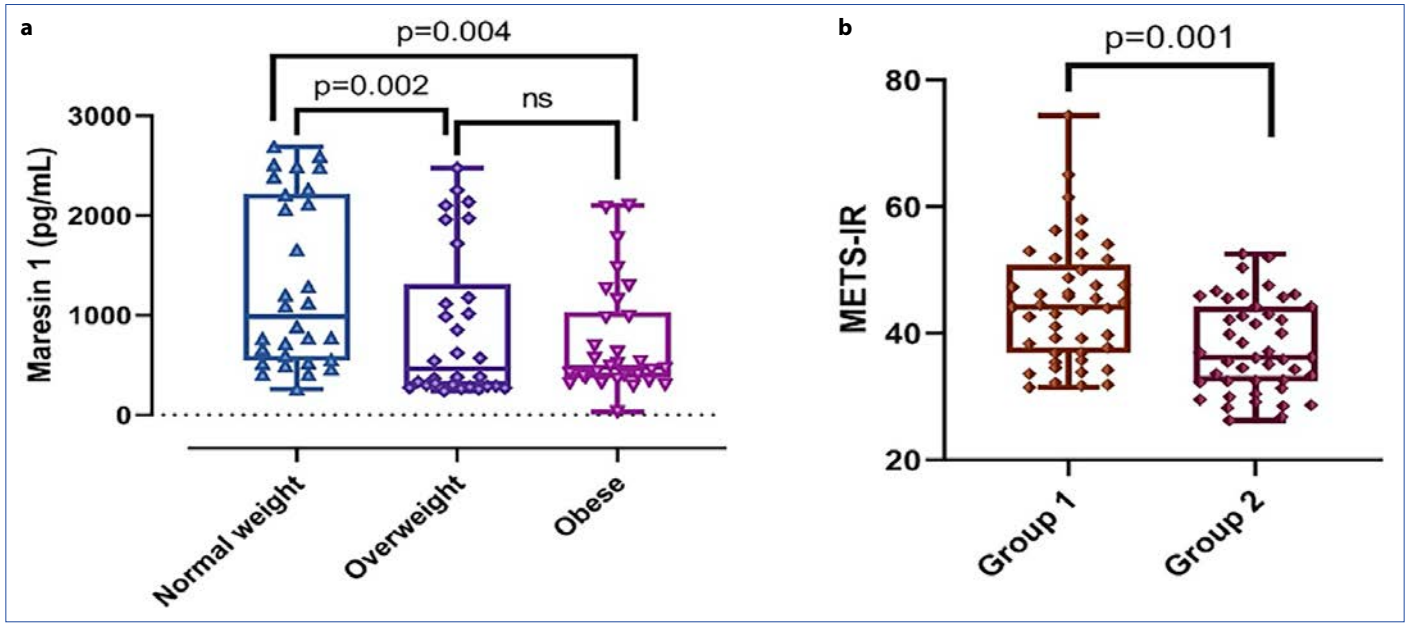

Figure 1. (a) Comparison of Maresin-1 levels among the three groups. (b) Comparison of METS-IR between the two groups based on the median Maresin-1 levels.

ns: Non-significant; Group 1: Maresin-1 <608 pg/mL; Group 2: Maresin-1≥ 608 pg/mL. METS-IR: Metabolic score for insulin resistance.

HOMA-IR, METS-IR, TyG-BMI, and HbA1c were higher in the MaR1<608 group than in the MaR1≥608 group, whereas only QUICKI was lower in the MaR1<608 group than in the MaR1≥608 group (Table 2 and Fig. 1b). A post-hoc power analysis was conducted for METS-IR between the two groups. The mean and standard deviation values were used to determine the effect size, which was determined to be Cohen's d=0.80, with an alpha of 0.05, the sample size for each group of 45, and two groups, yielding a power of 0.97. Given that the power output exceeded the ideal value of 0.80, it can be concluded that the power was sufficient.

MaR1 levels were negatively related to BMI (r=-0.495, p<0.001), BF% (r=-0.366, p<0.001), glucose (r=-0.294, p=0.005), insulin (r=-0.285, p=0.006), HOMA-IR (r=-0.318, p=0.002), METS-IR (r=-0.444, p<0.001), TyG-BMI (r=-0.427, p<0.001), and HbA1c (r=-0.247, p=0.019), whereas QUCKI (r=0.318, p=0.002) levels were positively correlated. The metabolic index with the highest correlation coefficient with MaR1 level was METS-IR (Table 3 and Fig. 2).

In the ROC analysis of the metabolic indicators for the identification of high levels of MaR1, METS-IR had the highest AUC value of 0.706 (95% CI=0.600–0.797), presenting 73.3% sensitivity and 57.8% specificity, p<0.001. TyG-BMI had an AUC value of 0.701 (95% CI=0.596–0.793), with 68.9% sensitivity and 71.1% specificity, p<0.001. HbA1c had an AUC value of 0.637 (95% CI=0.528–0.735), with 68.9% sensitivity and 57.8% specificity, p=0.021. HOMA-IR showed an AUC value of 0.635 (95% CI=0.527–0.734), with 60.0% sensitivity and 64.4% specificity, p=0.022. QUICKI performed the AUC value was 0.634 (95% CI=0.525–0.733), presenting 46.7% of sensitivity and 75.6% of specificity, p=0.022 (Table 4 and Fig. 3).

The findings of ordinal logistic regression exhibited an independent inverse association between MaR1 levels and BMI categories. In Model 1 (unadjusted), MaR1 was significantly associated with BMI categories, showing an odds ratio (OR) value of 0.9992 (95% CI:0.9987–0.9998, p=0.005). Adjusted for age, sex, and AI, this association remained significant, with an OR value of 0.9992 (95% CI:0.9986–0.9997, p=0.004), in Model 2. In Model 3, which included adjustments for age, sex, TyG and ALT, the association persisted, with an OR value of 0.9991 (95% CI:0.9985–0.9997, p=0.003) (Table 5).

Discussion

Lower serum MaR1 levels were found in obese and overweight subjects compared to normal-weight individuals, along with their correlation with BMI and BF%, indicating an association between MaR1 and obesity. This study found negative correlations between MaR1 levels and several metabolic parameters, including HOMA-IR, METS-IR, TyG-BMI, and HbA1c. Conversely, MaR1 levels were positively linked to QUICKI, suggesting an association between higher MaR1 levels and improved insulin sensitivity. Among the metabolic indicators examined, METS-IR demonstrated the strongest correlation with MaR1 levels (r=-0.444). ROC analysis revealed that METS-IR and TyG-BMI were the most effective parameters for identifying high MaR1 levels, with AUC of 0.706 and 0.701, respectively. METS-IR and TyG-BMI are useful surrogate markers for insulin resistance with significant associations with various cardiovascular conditions [17, 18]. These findings indicate that MaR1 is strongly associated with various insulin-resistance indices, including METS-IR and TyG-BMI, which are linked to high cardiovascular risk.

Table 2. Comparison of demographic and laboratory parameters between the two groups based on median Maresin 1 levels

Parameter	Maresin 1<608 pg/mL (n= 45)	Maresin 1≥608 pg/mL (n= 45)	p*
Age (years)	37.2±9.88	38.8±9.94	0.459
Gender (n, %)			
Male	10 (22.2)	11 (24.4)	0.803
Female	35 (77.8)	34 (75.6)	
Body mass index (kg/m^2)	29.4 (27.2–32.5)	25.6 (23.1–29.1)	**<0.001**
Body fat (%)	36.3±7.34	31.6±6.86	**0.002**
Glucose (mg/dL)	90.3±9.68	86.8±8.20	0.068
Insulin (mIU/L)	13.5 (10.1–22.3)	11.7 (8.16–14.8)	**0.036**
HOMA-IR	2.96 (2.30–5.58)	2.58 (1.62–3.19)	**0.028**
METS-IR	44.2 (36.9–50.4)	36.2 (32.4–44.3)	**0.001**
Triglyceride-glucose index	8.62±0.61	8.64±0.50	0.896
TyG-BMI	250 (217–291)	218 (190–263)	**0.001**
QUICKI	0.32±0.03	0.34±0.03	**0.019**
Mcauley index	6.09±1.60	6.42±1.45	0.314
Hemoglobin A1c (%)	5.69±0.48	5.50±0.39	**0.035**
Alanine transaminase (U/L)	19.0 (15.8–24.3)	18.0 (13.0–23.0)	0.175
Aspartate transaminase (U/L)	20.0 (18.0–24.3)	19.0 (16.8–24.3)	0.411
Cholesterol (mg/dL)	187 (157–214)	186 (163–222)	0.614
Triglyceride (mg/dL)	113 (91.3–185)	135 (93.8–187)	0.548
LDL-C (mg/dL)	109 (92.5–138)	109 (89.0–145)	0.981
HDL-C (mg/dL)	49.0 (40.8–58.0)	49.0 (41.8–56.5)	0.657
TG/HDL-C	2.60 (1.55–4.64)	2.37 (1.83–3.56)	0.971
Castelli risk index I	3.88 (3.06–4.72)	3.76 (3.10–4.27)	0.625
Castelli risk index II	2.44 (1.88–3.17)	2.22 (1.81–2.82)	0.503
Atherosclerotic index	2.88 (2.06–3.72)	2.76 (2.10–3.27)	0.625

*: p<0.05: Statistically significant. HOMA-IR: Homeostatic model assessment of insulin resistance; METS-IR: Metabolic score for insulin resistance; TyG-BMI: Triglyceride-glucose index and body mass index; QUICKI: Quantitative insulin sensitivity check index; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG/HDL-C: Triglycerides to high-density lipoprotein cholesterol ratio.

Insulin resistance serves as a pivotal factor in the emergence of numerous metabolic disorders such as obesity, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD) [19]. Studies investigating the relationship between MaR1, obesity, and insulin resistance in the human population are notably limited in the current literature. T2DM patients, particularly those with diabetic foot ulcers, exhibited lower plasma MaR1 concentrations compared to individuals with normal glucose tolerance. Reduced MaR1 levels were closely linked to obesity, reduced insulin secretion, and elevated insulin resistance (HOMA-IR). MaR1 levels were positively related to beta-cell function (HOMA-β), acute insulin response, and HDL-C [20]. In a study, no significant differences in MaR1 levels were observed between individuals with mild and morbid obesity. However, differences in diabetes remission and the capacity for inflammation resolution following surgery were identified as significant factors influencing MaR1 levels. Specifically, diabetic patients who failed to achieve remission experienced a substantial impairment in MaR1 production. Sufficient MaR1 production was linked to the control of inflammation and improved insulin sensitivity. Therefore, therapies aimed at enhancing MaR1 biosynthesis might represent potential strategies against insulin resistance [6]. MaR1 activates brown adipose tissue while causing browning of white adipose tissue, suggesting that this molecule might

Table 3. Significant correlations between Maresin 1 and the other variables in all groups

Parameter	Maresin 1 (pg/mL)	
	r	p
Body mass index (kg/m^2)	-0.495	<0.001
Body fat (%)	-0.366	<0.001
Glucose (mg/dL)	-0.294	0.005
Insulin (mIU/L)	-0.285	0.006
HOMA-IR	-0.318	0.002
METS-IR	-0.444	<0.001
TyG-BMI	-0.427	<0.001
QUICKI	0.318	0.002
Hemoglobin A1c (%)	-0.247	0.019

r: Spearman correlation. HOMA-IR: Homeostatic model assessment of insulin resistance; METS-IR: Metabolic score for insulin resistance; TyG-BMI: Triglyceride-glucose index and body mass index; QUICKI: Quantitative insulin sensitivity check index.

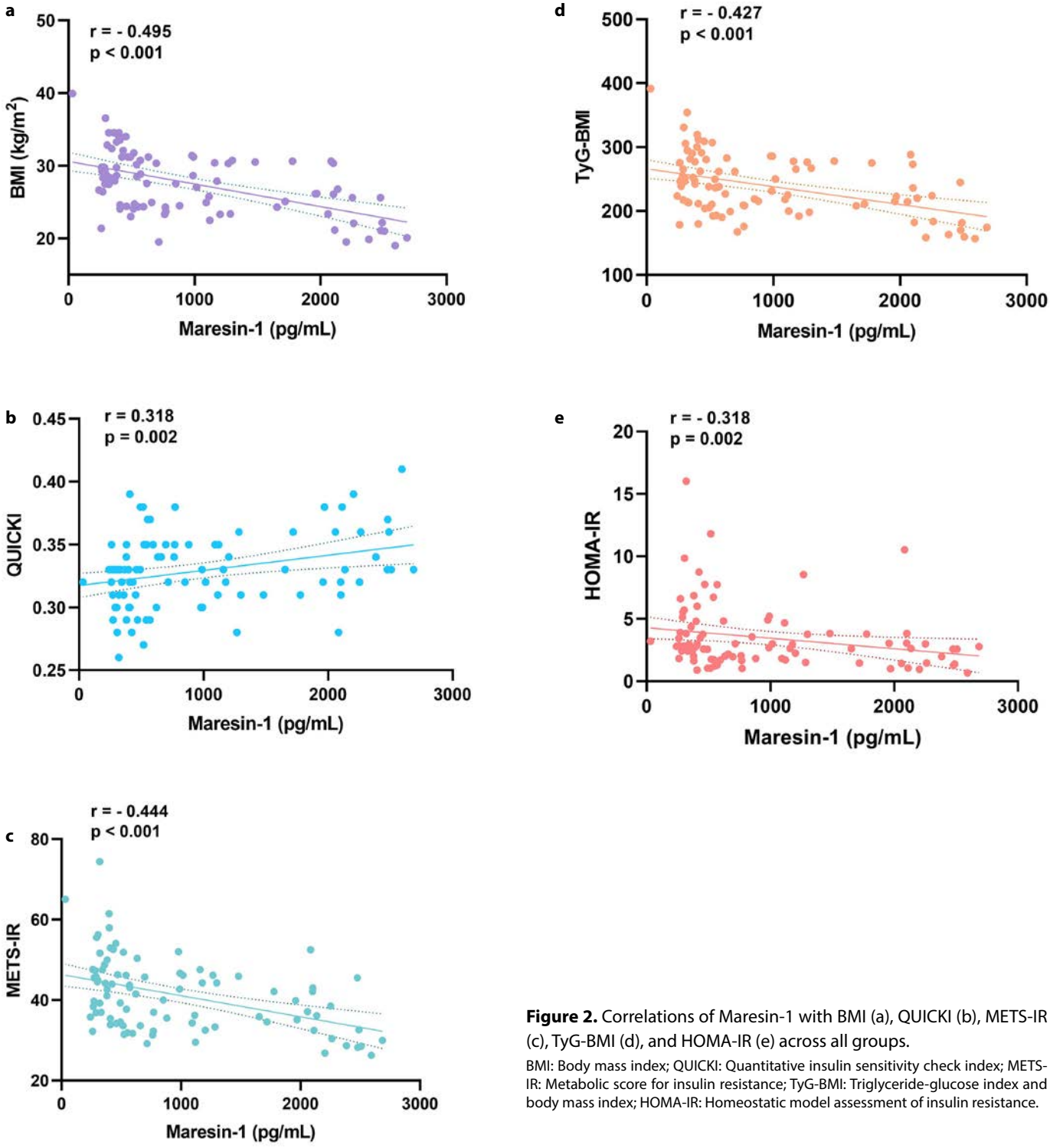

Figure 2. Correlations of Maresin-1 with BMI (a), QUICKI (b), METS-IR (c), TyG-BMI (d), and HOMA-IR (e) across all groups.

BMI: Body mass index; QUICKI: Quantitative insulin sensitivity check index; METS-IR: Metabolic score for insulin resistance; TyG-BMI: Triglyceride-glucose index and body mass index; HOMA-IR: Homeostatic model assessment of insulin resistance.

contribute to the control of adipokine synthesis and release in obese individuals [21, 22]. Circulating MaR1 concentrations were found to be markedly reduced in individuals with NAFLD. MaR1 levels were inversely correlated with BMI, glucose, ALT, GGT, and TG levels. Conversely, MaR1 levels were positively and independently associated with AST/ALT ratio, albumin level, albumin-globulin ratio, and HDL-C level. The proportion of patients diagnosed with NAFLD showed a progressive decline across ascending MaR1 quartiles. This relationship points to MaR1's potential role in metabolic health and inflammation, as decreased MaR1 might contribute to metabolic dysfunctions associated with higher BMI [23]. Our research revealed no association between MaR1 concentrations and the analyzed lipid measurements and parameters.

Table 4. ROC analysis of metabolic indicators for identifying high Maresin 1 levels

Parameter	AUC (95 CI%)	Cut-off	Sensitivity	Specificity	LR (+)	LR (–)	p
METS-IR	0.706 (0.600–0.797)	≤43.0	73.3%	57.8%	1.74	0.46	<0.001
TyG-BMI	0.701 (0.596–0.793)	≤236	68.9%	71.1%	2.38	0.44	<0.001
Hemoglobin A1c (%)	0.637 (0.528–0.735)	≤5.70	68.9%	57.8%	1.63	0.54	0.021
HOMA-IR	0.635 (0.527–0.734)	≤2.69	60.0%	64.4%	1.69	0.62	0.022
QUICKI	0.634 (0.525–0.733)	>0.33	46.7%	75.6%	1.91	0.71	0.022

ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval; LR: Likelihood ratio; METS-IR: Metabolic score for insulin resistance; TyG-BMI: Triglyceride-glucose index and body mass index; HOMA-IR: Homeostatic model assessment of insulin resistance; QUICKI: Quantitative insulin sensitivity check index.

Table 5. Ordinal logistic regression analysis results

Regression model	Maresin-1 (pg/mL)				
	Estimate	SE	Wald	OR (95%CI)	p
Model 1	-0.001	0.000	7.974	0.9992 (0.9987–0.9998)	**0.005**
Model 2	-0.001	0.000	8.341	0.9992 (0.9986–0.9997)	**0.004**
Model 3	-0.001	0.000	8.672	0.9991 (0.9985–0.9997)	**0.003**

Model 1: Unadjusted; Model 2: Age, sex, AI; Model 3: Age, sex, TyG, ALT. SE: Standard error; OR: Odds Ratio; CI: Confidence interval; TyG: triglyceride glucose index; ALT: alanine aminotransferase.

MaR1 enhanced insulin sensitivity and reduces inflammation in the white adipose tissue of obese mice by modulating inflammatory markers and activating insulin signaling pathways, such as Akt and AMPK. MaR1 treatment has the potential to serve as an effective therapeutic approach aimed at improving insulin sensitivity in obese mouse models, thereby addressing the key metabolic dysfunctions associated with obesity and potentially mitigating the risk of related complications [22, 24]. MaR1 has been demonstrated to modulate the expression of adipokines in obese models. In cultured human adipocytes, MaR1 increased the basal expression of adiponectin, leptin, dipeptidylpeptidase 4, cardiotrophin 1, and irisin while effectively counteracting the effects of TNF-α. This regulatory mechanism could counteract inflammation and improve insulin sensitivity. The study suggested that MaR1 tissue-specific actions could be harnessed to improve metabolic profiles by reducing inflammation and restoring healthy adipokine levels in obesity [25]. Additionally, MaR1 suppresses lipid accumulation and endoplasmic reticulum stress in hepatocytes, resulting in reduced hepatic steatosis and improved lipid metabolism in high-fat diet-fed mice [26]. Mitochondrial damage in liver cells is frequently observed in fatty liver disease associated with metabolic dysfunction. MaR1 enhanced liver mitochondrial and metabolic performance, protecting liver cells from mitochondrial impairment that was induced by factors promoting obesity and fibrosis [27]. Preclinical studies have suggested that SPMs could be effective in preventing and managing cardiovascular disease by enhancing endogenous SPM production through polyunsaturated fatty acids or by administering synthetic SPM analogues [4]. Generally,

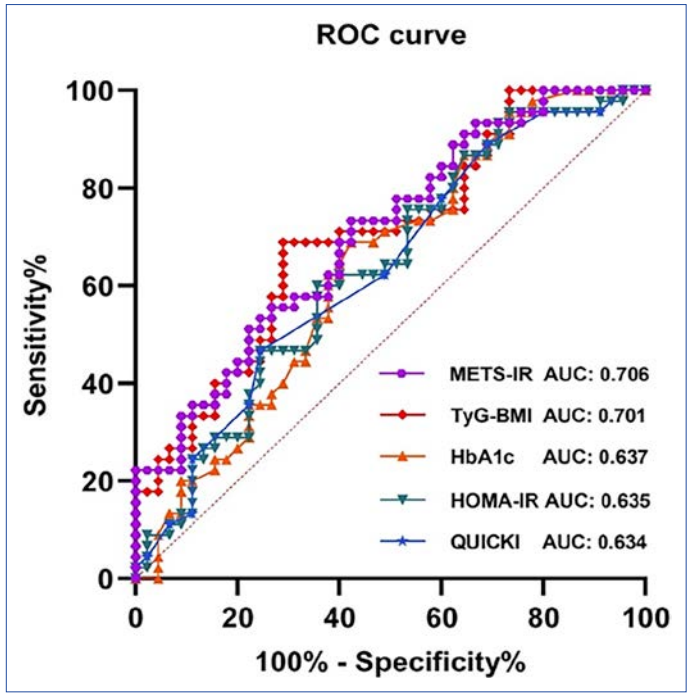

Figure 3. ROC analysis of metabolic indicators for identifying high Maresin 1 levels.

ROC: Receiver operating characteristic; METS-IR: Metabolic score for insulin resistance; TyG-BMI: Triglyceride-glucose index and body mass index; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic model assessment of insulin resistance; QUICKI: Quantitative insulin sensitivity check index.

MaR1 and its related metabolites have cardiovascular protective functions and/or inhibit the progression of cardiovascular

diseases [28]. Since most of the studies on MaR1 and obesity are experimental, conclusive results can be achieved through data gathered from more comprehensive human studies.

Although the relationship between MaR1 and lipid and glucose indicators has been demonstrated on a molecular basis in mouse models, research exploring this connection in humans remains limited. The current literature does not directly investigate the association between MaR1 and METS-IR, TyG-BMI, or QUICKI indices. METS-IR index, which combines fasting triglyceride, glucose, BMI and HDL-C, is now recognized as a more accurate tool for evaluating insulin sensitivity. METS-IR is associated with various cardiovascular events, and its ability to predict inflammatory activity and endothelial dysfunction has been emphasized [29, 30]. In non-diabetic Korean individuals, a high METS-IR score demonstrated a significant prognostic value for future occurrences of ischemic heart disease [31]. The TyG-BMI index combines the TyG index, which reflects glucose and triglyceride levels, with BMI, which is a measure of adiposity. This combination seems to offer a more extensive evaluation of metabolic status than the TyG index or BMI alone [32]. According to a cohort investigation, TyG-BMI emerged as the most effective indicator for predicting metabolic syndrome in male subjects [33]. TyG-BMI and METS-IR were shown to be strongly associated with NAFLD and were identified as the most valuable IR-related indicators with high discriminatory ability for NAFLD screening [34].

This study has some limitations, including its single-center cross-sectional design. Inflammatory parameters, including cytokines, which could have provided insights into the relationship between MaR1 and inflammation in obesity, have not been evaluated. Although liquid chromatography–mass spectrometry (LC-MS) is widely used for the analysis of SPMs such as Maresin 1 due to its high specificity, precision, and accuracy in lipid quantification, ELISA was chosen for this study because of its sensitivity, methodological simplicity, and feasibility, as LC-MS was not available in our laboratory [35]. Prospective follow-up to predict obesity-related vascular events or morbidity could not be performed.

Conclusion

Our study demonstrated significant associations between MaR1 levels and insulin resistance indices, such as METS-IR and TyG-BMI, which are also indicative of cardiovascular risk in obese patients. Furthermore, ordinal regression analysis revealed an independent negative relationship between the MaR1 levels and obesity. This investigation addresses a crucial void in current research by offering novel perspectives on the connection between MaR1 and these key insulin resistance indices. Research into the role of lipid mediators like MaR1 in resolving inflammation and improving insulin sensitivity could provide new therapeutic avenues. To fully elucidate the metabolic mechanisms associated with obesity and to explore the therapeutic efficacy of MaR1 in humans, more extensive clinical investigations are essential.

Ethics Committee Approval: The study was approved by The Firat University Non-interventional Research Ethics Committee (No: 2023/10-23, Date: 27/07/2023).

Authorship Contributions: Concept – L.D., M.Y.; Design – L.D., M.Y.; Supervision – L.D.; Materials – M.Y., M.A.S.; Data collection &/or processing – M.Y., M.A.S.; Analysis and/or interpretation – L.D., R.F.A.; Literature search – L.D., M.Y., M.A.S., R.F.A.; Writing – L.D., M.Y., R.F.A.; Critical review – L.D., M.Y., M.A.S., R.F.A.

Conflict of Interest: The authors declare that there is no conflict of interest.

Use of AI for Writing Assistance: No AI technologies utilized.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

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